Rejection under 35 U.S.C. § 112, first paragraph

The rejection alleges that claims 37 and 38 were not described in the specification in such a way as to show that Applicants had possession of the claimed invention. The rejection alleges that the specification does not disclose a representative number of species of the PI-kinase inhibitors that function to decrease cell proliferation of ovarian cells. Furthermore, the rejection argues that the description in the specification directed to identifying PI kinase inhibitors (including the passages teaching how to assay for PI kinase activity and assays to assess proliferation and viability of ovarian cancer cells that have been treated with PI kinase inhibitors), and administration of such compounds does not adequately support the claimed invention. The rejection argues that none of these teachings "make the connection" between the ability of a compound to inhibit PI kinase and the inhibition of PI kinase resulting in the inhibition of ovarian cancer cell proliferation in a patient.

Claims 36-39 were rejected as allegedly not enabled. (Note that claim 36 was canceled in Applicants' response filed December 15, 2001). The rejection contends that it would require undue experimentation to determine which compounds that inhibit PI kinase activity and ovarian cancer cell proliferation *in vitro*, would also inhibit ovarian cancer cell proliferation *in vivo*. The rejection also contends that showing that one specific compound that inhibits PI kinase activity and ovarian cancer cell proliferation *in vitro* is not evidence that all compounds that inhibit PI kinase activity will also decrease ovarian cancer cellular proliferation.

The Examiner thus appears to be concerned that the claims encompass PI kinase inhibitors that are not explicitly disclosed in the specification and that one of skill could not identify others in the absence of undue experimentation. Since the written description and enablement rejections are closely related, they are addressed together, below. The enablement rejection regarding the correlation of *in vitro* activity with efficacy *in vivo* is further addressed in the last section of the response to the §112 rejections.

As noted above, Applicants invention is the discovery PI kinase plays a role in ovarian cancer proliferation. The invention is ***not*** the discovery of PI kinase inhibitors. Rather, the inventors have discovered that agents that inhibit PI kinase activity inhibit ovarian cancer cell proliferation. This association between PI kinase activity and the proliferation of ovarian cancer cells had not been previously described. As shown in Example 1, Applicants discovered that PIK3CA is amplified in ovarian cancer and further, that PIK3CA is overexpressed in ovarian cancer

(Example 2, page 30). Applicants also showed that ovarian cancer cells with increased PIK3CA expression also exhibited increased PI kinase activity (Figure 3), and lastly, that a specific inhibitor of PI kinase, inhibited ovarian cancer cell proliferation.

In light of these observations, the inventors recognized that inhibition of PI kinase would have therapeutic benefits. Since PI kinases are well studied and inhibitors of these enzymes are known, the inventors recognized that any of a number of means of inhibiting the activity of PI kinase could be used in the invention. Indeed, the specification provides examples of such means, as noted in Applicants response filed December 15, 2000.

Applicable law

A review of the case law reveals that there are situations in which an applicant can properly obtain method claims directed to medical treatments based on the administration of a chemical agent that is defined solely by function and not structure.

As an initial matter, the courts have described the essential question to be addressed in a description requirement issue in a variety of ways (*see,* MPEP at § 2163.02). An objective standard for determining compliance with the written description requirements is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented that what is claimed." *In re Gosteli,* 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). As explained herein, the specification provides an adequate disclosure to convey the invention to one of skill in the art, in the absence of a structural definition of an inhibitor of PI kinase activity.

Functional language is proper for non-inventive aspects of the invention

Since the invention is not the discovery of inhibitors, but their use in new therapeutic methods, identification of the inhibitors by their function is entirely proper. The courts have specifically held that rejection of composition claims under §112, first paragraph are improper when the functional language is not used to describe the point of novelty. *See, e.g., In re Fuetterer*, 132 USPQ 217 (CCPA 1963). In *Fuetterer*, the invention was a rubber stock composition useful in producing tire treads. The claims included a recitation of "an inorganic salt capable" of maintaining a homogeneous distribution of another component in the composition. The disclosure listed the function desired and identified four members of the class of inorganic salts having that function. In holding that the description requirement was satisfied the court focused on the fact that the invention

claimed was the combination, not the fact that certain salts have colloid suspending properties. The court went on to state:

> The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them *per se*, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by the appellant in his disclosure. Id. at 223. (emphasis added)

As with the inorganic salts of *Fuetterer*, the PI kinase inhibitors recited in the claimed methods are defined by their ability to carry out a particular function (inhibit the activity of a certain enzyme), not their chemical structure. The particular structure of the inhibitor used is not critical to the invention so long as the desired function is achieved. The ruling in *Fuetterer* makes clear that the identification of other inhibitors not specifically disclosed in the present application are properly within the scope of the applicants contribution to the art. Thus, the claims should not be so restricted that they can be avoided simply by using an inhibitor different from those specifically exemplified in the application.

A second CCPA decision (*In re Herschler* 200 USPQ 711 (CCPA 1979)) is further on point. That claims at issue were for the use of dimethyl sulfoxide (DMSO) to enhance tissue penetration of physiologically active steroidal agents. The claims were directed to the delivery of all physiologically actives steroids while the great grandparent specification which was relied on for support provided only a single example demonstrating the efficacy of the claimed methods.

Based on the record before them, the court concluded that one of skill would have expected other steroids to function equally well in the claimed methods because steroids, when considered as a class of chemicals delivered using DMSO, should behave quite similarly. The court, therefore, reversed the Patent Office's rejection of these claims reasoning that, because the invention was not the discovery of novel steroidal agents but the delivery of the agents in combination with DMSO, the demonstration of the efficacy of the invention with a number of steroidal agents was not required under §112, first paragraph.

Similarly, in the present case, the claimed invention is not the discovery of a particular PI kinase inhibitor, but the discovery of a new method of using them to treat ovarian

cancer. Based on the holding in *Herschler*, Applicants have provided sufficient description and support to fulfill the requirements of §112, first paragraph.

Undue experimentation is not required to identify inhibitors useful in the invention

The Court of Appeals for the Federal Circuit has long recognized that in a rejection for undue experimentation that: "the key word is 'undue', not 'experimentation'". *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). This decision makes clear that a considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance respect to the direction in which the experimentation should proceed. The MPEP reiterates this same conclusion (*see*, MPEP § 2164.06). In the present case, an assertion of undue experimentation must be supported by an explanation as to why the assays described in the specification could not be used in a routine screen to identify inhibitors of PI kinase activity and as to why inhibitors of PI kinase activity would not be expected to prevent ovarian cancer cell proliferation. The Examiner has not made such a showing.

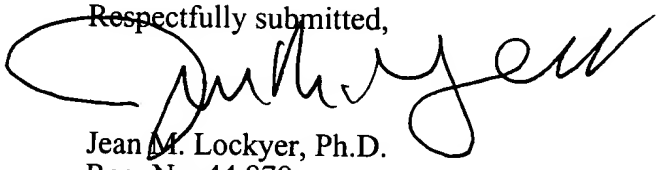
The rejection did suggest that observation of inhibition of ovarian cancer cell proliferation by an inhibitor of PI kinase activity *in vitro* is inadequate to support a use *in vivo*. However, as previously noted (*see,* Applicants' response filed December 15, 2000), Applicants have provided adequate guidance not only for the identification and selection of PI kinase inhibitors, but also for administering such inhibitors to inhibit proliferation of ovarian cancer cells. Indeed, a publication that further validates that the application is enabling both *in vitro* and *in vivo* is attached hereto as Appendix A (Hu *et al., Clin. Cancer Res.* 6:880-886, 2000). In this study, Hu *et al.* administered an inhibitor of PI kinase activity, LY294002, to athymic mice that had been inoculated with human ovarian carcinoma cells. The results showed that treatment with LY294002 inhibited tumor growth and ascites formation. Thus, one of skill in the art, can without undue experimentation extrapolate the *in vitro* results to an *in vivo* use as taught in the specification and practice the claimed invention.

In view of above remarks, Applicants respectfully requested withdrawal of the rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

37. (two times amended) A method of inhibiting the pathological proliferation of ovarian cancer cells in a patient, the method comprising administering a therapeutically effective dose of an inhibitor of PI kinase to the patient, wherein the inhibitor inhibits PI kinase enzymatic activity.

38. (two times amended) The method of claim 37 [36], wherein the inhibitor of PI kinase is a non-peptidic inhibitor of enzyme activity.

39. (amended) The method of claim 38, wherein the non-peptidic inhibitor is LY294002.

40. (canceled)